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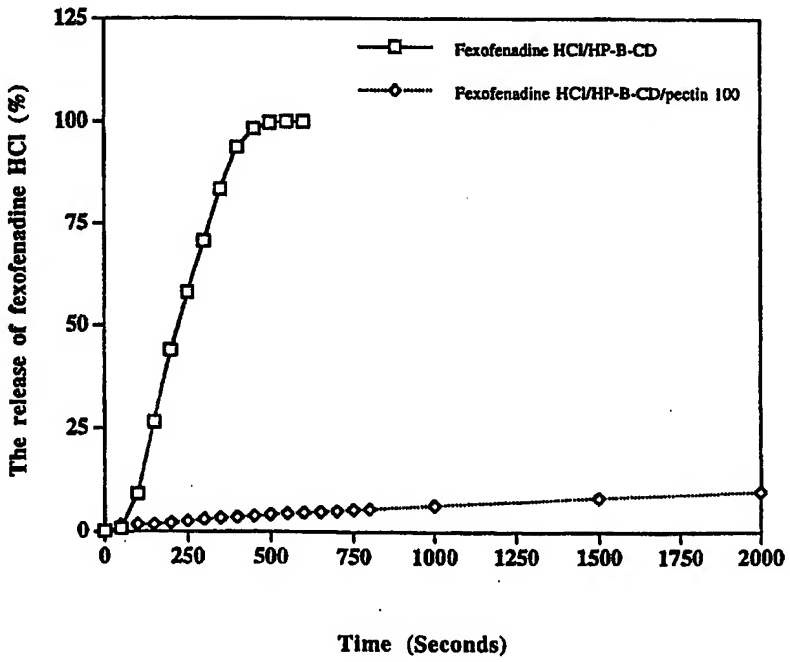

(57) Abstract

Liquid pharmaceutical compositions for administration to a mucosal surface, comprising a therapeutic agent and a pectin with a low degree of esterification are described. Such compositions gel, or can be adapted to gel, at the site of application in the absence of an extraneous source of divalent metal ions.

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IMPROVED DELIVERY OF DRUGS TO MUCOSAL SURFACES

This invention relates to an improved system for the delivery of drugs to mucosal surfaces such as the nose, the eye, the vagina, the rectum and the back of the throat.

Administration of therapeutic agents to mucosa is well known in the art.

A variety of drugs may be administered to the nose, including those intended for the local treatment of nasal diseases, nasal vaccines, and those intended for systemic circulation. Because the nose has a reasonable surface area and a good blood supply, certain lipophilic drugs, such as nicotine and propranolol, can be absorbed rapidly into the blood, resulting in a bioavailability which is similar to that seen with intravenous injection. More polar drugs are less well absorbed, though absorption may be improved by the use of enhancing agents such as surfactants, powders such as microcrystalline cellulose, gelling microspheres (eg. starch), and the bioadhesive polymer, chitosan. Examples of these systems are well known in the art and have been reviewed by Illum and Fisher in "*Inhalation Delivery of Therapeutic Peptides and Proteins*", Adjei and Gupta (eds.) Marcel Dekker Inc., New York (1997) 135-184.

In a similar fashion, it is useful to deliver therapeutic agents, such as drugs and vaccines, to the vaginal cavity for a systemic effect or for the local treatment of diseases (particularly infectious diseases such as candidiasis and bacterial vaginitis) as well as for prophylaxis of diseases (e.g. HIV). Locally acting formulations may also be used to deliver contraceptive and spermicidal agents.

Drugs may also be administered to mucosa in the eye and the rectum in order to achieve local effects or for systemic activity.

Considerable advantages in terms of improved efficacy are expected to be gained if a nasally administered formulation were capable of retaining a drug, a vaccine, or DNA intended for local effect, in the nose for relatively long time periods. Previous workers have used a variety of strategies for this purpose.

For example, Illum and others found that biodegradable microspheres based on materials such as starch could delay clearance to a period of hours as compared to a normal half life of clearance of about 10 to 15 minutes (Illum *et al*, Int. J. Pharm., 39 (1986) 189-199). Surprisingly, such systems were also found to give an improved absorption by affecting the integrity of the tight junctions of the epithelial cells in the nasal cavity and are expected therefore to be best suited to drugs acting systemically.

Similarly, Illum and others have shown that the bioadhesive material chitosan can modify mucociliary clearance with an increase in drug absorption (Illum *et al*, Pharm Res., 11 (1994) 1186-1189).

It would be most beneficial, due to ease of use and of administration, to have available a simple solution spray system that was suitable for the administration of drugs to the nose and, better still, for the drugs administered *via* such a system to have a long retention in the nasal cavity. The skilled person may envisage various strategies to this end, including the use of pharmacological agents that decrease mucociliary clearance by a

direct effect on the action of cilia, such as cocaine, as well as formulation methods such as environmentally-responsive gels.

Liquids that gel in response to a change in environment are known to those skilled in the art. The environmental change can be temperature, pH or ionic strength or a combination of these factors. Examples of all of these systems can be found in the prior art literature (see, for example, the smart hydrogel from Gelmed as described by Potts *et al* in *Proceed. Intern. Symp. Control Rel.*, **24**, 335 (1997)). However, the majority of these have been found to be unsuitable for nasal use in man because of factors such as irritation, discomfort (eg. administration of cold solutions), mucosal damage, an unwanted enhancement of drug absorption into the systemic circulation, and many are unavailable due to lack of regulatory approval.

In summary, it would present considerable advantages to provide a single component nasal delivery system, which was in the form of a liquid for ease of administration, and in particular one that gelled in the nose upon contact with the nasal tissues, which could be used to administer, and to modify absorption characteristics, of drugs (therapeutic agents) intended to act locally or systemically. It would also be desirable to provide a system which is well accepted by patients, does not enhance the absorption of drug intended for a local effect into the systemic circulation (as this could lead to side effects), and comprises materials that are approved by regulatory authorities.

Those skilled in the art will appreciate that there are similar problems to be solved in respect of drug delivery for the improved treatment of conditions that affect the vaginal cavity, the rectum, the eye, and the back

of the throat, as well as for the improved delivery of vaccines to the local lymphoid tissue, or for the improved delivery of DNA for the transfection of epithelial cells.

For example, drugs intended for the treatment of vaginal infections, or drug free formulations intended to act as vaginal moisturising agents (especially useful in post-menopausal conditions), should spread well in the vaginal cavity and be retained for long periods of time. However, it has been reported that so-called bioadhesive formulations that are intended to be retained in the vaginal cavity for days can be expelled rapidly, with more that 80% of the dose leaving the vagina in less than 2 hours (Brown *et al*, 14, 1073 (1997)). Thus, it would be advantageous to provide a single component liquid composition that could be inserted into the vagina as a simple liquid and that gelled under the local environmental conditions to give good retention.

For rectal enemas, it would be most beneficial if the liquid enema formed a gel once applied, ensuring close contact with the local environment and preventing early discharge.

Similar problems may be identified in respect of administration to the eye, by virtue of the fact that liquid formulations are rapidly cleared from the eye through drainage down the naso-lacrymal duct. A single component liquid composition that gelled upon application to the eye would be advantageous for the treatment of conditions such as eye infections and inflammation.

Pectins are materials which are found in the primary cell wall of all green land plants. They are heterogeneous materials, with a polysaccharide

backbone that is uniform as α-1,4-linked polygalacturonic acid. Various neutral sugars have been identified in pectins such as xylose, galactose, rhamnose, arabinose.

A critical property of pectins, which is known to affect their gelation properties, is the extent to which the galacturonic acid units are esterified. The degree of esterification (DE) of pectins found naturally can vary considerably (from 60 to 90%). The term DE is well understood by those skilled in the art and may be represented as the percentage of the total number of carboxyl groups which are esterified,. or as the methoxyl content of the pectin. The respective theoretical maximum for each is 100% and 16% respectively. DE as used herein refers to the total number of carboxyl groups which are esterified. Low DE pectins (ie. those having less than 50% esterification) are usually prepared by the de-esterification of extracted pectins, normally on a bench scale, by way of an enzymatic process, or, on an industrial scale, by the treatment with acid or ammonia in an alcoholic heterogeneous medium. For pectins with a low degree of methoxylation (DM; less than 45%) the gelation properties are known to depend on the DM and the molecular weight of the pectin. The chemistry of low methoxyl pectin gelation is described by Axelos and Thibault in "*The Chemistry and Technology of Pectin*", Academic Press, New York, pp. 109-118, (1991).

Various prior art documents discuss the potential use of pectin as a bioadhesive and gelling material. Studies by Smart *et al*, J. Pharm. Pharmacol. **36**, 295 (1984) in relation to the adhesiveness of various materials to mucus have shown that pectin is poorly adhesive in *in vitro* tests. A tablet capable of adhering to the mucus membrane containing pectin has been described in EP 306 454. Oechslein *et al* (Int. J. Pharm.,

139, (1994), 25-32), have described the potential of various powder formulations to enhance the nasal absorption of the somatostatin analogue peptide octreotide. Pectin (type FPA) powder was used, and gave rise to an increase in the absolute bioavailability of the drug as compared to the drug administered in a saline solution. In none of these documents was the use of a solution formulation containing a pectin with a low DE, or a pectin that gels in contact with nasal secretions, described.

Pectin has also been studied as a mucoadhesive ophthalmic material by Chetoni *et al* (Bull. Chem. Farm., 135, 147 (1996)). Salt complexes of drugs with pectin for administration to the oral mucosa as patches have been described by Burgalassi *et al*, World Meet. Pharm. Biopharm. Pharm. Technol., (1995), p. 839, APGI, Paris. Popovici and Szasz (in "*Buccal and Nasal Administration as Alternatives to Parenteral Administration*", Minutes of a European Symposium (1992), Duchene, D., Ed., Sante, Paris, France. p. 292-6) have described mucoadhesive hydrogels containing cellulose and pectin and a bivalent cation in the form of magnesium. The use of a low DE pectin as a solution that would gel in contact with mucosal surfaces was not described in any of these documents.

US 4,826,683 describes a nasal decongestant containing vegetable oil, aloe vera, zinc, vitamin C, vitamin A, vitamin E, vitamin B6, biotin and fruit pectin. The content of fruit pectin was to a maximum of 2 g per litre. The solubilised fruit pectin supplied by General Foods under the trade name "Certo" was preferred. JP 62236862 describes an artificial mucus composed of a mixture of a spinnable water soluble polymer and a polysaccharide, protein or vinyl polymer. Pectin is listed as a suitable polysaccharide, though the type of pectin is not specified.

US 5,147,648 (EP 289 512) describes a pharmaceutical formulation made from at least two components which, when added separately, can form a gel for treating a mucosa. The two components are applied separately to the same area of a mucous membrane. The components may be added simultaneously or sequentially. One of the gel forming solution components includes a calcium salt (eg. calcium gluconate) and the other may include a pectin. There is no suggestion in this prior art document that a solution comprising pectin may be administered as a single component, in the absence of a separately applied solution of calcium ions, which will gel once in contact with the mucosa.

US 5,318,780 describes aqueous pharmaceutical vehicles containing two components, a film forming polymer (eg. pectin) and an ionic polysaccharide, which are then gelled *in situ* by contacting the mixture with a counter-ion. Polygalacturonic acids such as pectin are mentioned in an extensive listing of representative useful polymers for application in the eye as corneal mastis protective corneal shields. No examples of the use of a pectin solution alone, nor of pectins with a low DE, or pectins that would gel in contact with the mucosa, are disclosed.

The preparation of pectin beads by ionotropic gelation has been described by Aydin and Akburfa (1996) Int. J. Pharm., **137**, 133-136.

In summary, although it is known in the art that all pectins will form gels in the presence of calcium ions, for the pectins employed previously in pharmaceutical systems to be applied to mucosal surfaces, it has been hitherto understood that high levels of calcium are needed, which levels are well above physiological concentrations. This has necessitated the

utilisation of pectin systems which are applied either in the form of preformed gels, or before or after the addition of exogenous calcium in order to produce a gel *in situ*. That liquids (especially solutions) comprising low DE pectins may be applied as such, and may gel upon, or just after, application to mucosa is neither described nor suggested in any of the aforementioned prior art documents. Further, the importance of the DE of pectin upon such gelation properties is not mentioned in any of these prior art documents.

We have now found, surprisingly, that certain pectin materials, namely those with a low DE, may be administered in the form of single component, simple liquid formulations (i.e. in an aqueous carrier) which will gel, or can be readily adapted to gel, upon application to mucosa in the nasal, rectal and vaginal cavities, in the eye, or at the back of the throat. We have also found, surprisingly, that gelation may occur at physiologically acceptable pH values in the presence of very much reduced calcium concentrations, ie. those which can be found physiologically in the nasal secretions, as well as in the vaginal lumen, the rectal cavity and the tear fluid of the eye.

According to a first aspect of the invention there is provided a single component liquid pharmaceutical composition for administration to a mucosal surface comprising a therapeutic agent, a pectin with a low DE and an aqueous carrier, that gels or can be adapted to gel at the site of application.

We have found, in particular, that such compositions gel, or can be adapted to gel, at the site of, and upon, or just after, application to a mucosal surface in the absence of an extraneously (ie. separately and/or

independently) applied (simultaneously or sequentially) solution of calcium (or other divalent metal) ions. There is thus provided a single component liquid pharmaceutical composition for application directly to a mucosal surface comprising a therapeutic agent, a pectin with a low DE and an aqueous carrier, which composition is adapted to gel at the site of application in the absence of an extraneous source (eg. solution) of divalent metal ions applied to the same site.

According to a further aspect of the invention, there is provided a kit of parts comprising a liquid pharmaceutical composition for administration to a mucosal surface, comprising a therapeutic agent, a pectin with a low DE and an aqueous carrier, provided that the kit does not comprise a solution of divalent metal ions to be added extraneously to said surface.

In particular, there is provided a kit of parts comprising a liquid pharmaceutical composition for administration to a mucosal surface, which composition comprises a therapeutic agent, a pectin with a low DE and an aqueous carrier, and which kit of parts is packaged and presented with instructions to administer said composition to said surface in the absence of an extraneous source of divalent metal ions.

The liquid pharmaceutical compositions for administration to mucosal surfaces comprising therapeutic agent, low DE pectin and aqueous carrier, which are, or are to be, administered as a single component, and which gel, or are adapted to gel, in the absence of an extraneous source of divalent metal ions are referred to hereinafter as "the compositions of the invention".

By "liquid" composition, we mean a composition which is in the form of a mobile fluid upon application to the mucosa. The compositions of the invention are in the form of an aqueous formulation comprising a solution, a suspension, or an emulsion, including pectin and therapeutic agent, in water. The compositions of the invention will gel, or may be adapted to gel, upon, or shortly (eg. up to 5 minutes) after, application, to a form a solid or semi-solid gel material, which gel is suitable to provide a retaining effect at the site of administration.

By "degree of esterification (DE)", we mean the percentage of galacturonic acid units which are esterified, for example as described in the article by Walter in "*The Chemistry and Technology of Pectin*", Academic Press, New York (1991), p. 192. By "low DE", we mean a pectin in which less than 50%, and more preferably less than 35%, of the galacturonic acid units are esterified.

By "extraneous source" of divalent metal ions, we include a separate and/or independent (ie. exogenous) source of such ions. Ions which are present in a gel resulting from administration of a composition of the invention to a mucosa are not derived from either the composition, or from the bodily secretions of the patient to which the composition is to be applied (eg. endogenous ions derived from nasal secretions, tear fluid, etc.). Divalent metal ions which may be mentioned include calcium ions.

According to a further aspect of the invention, there is provided a pharmaceutical gel composition obtainable by applying a liquid composition, comprising a therapeutic agent, a pectin with a low DE and an aqueous carrier, to a mucosal surface of a mammalian patient in the

absence of extraneous application of a solution of divalent metal ions to said surface.

The gels so formed upon contact with mucosal surfaces will contain only endogenous divalent metal ions (i.e. those derived directly from bodily secretions) and will not include exogenous divalent metal ions (i.e those derived from an extraneous source). According to a further aspect of the invention there is provided a pharmaceutical gel composition, which gel comprises a therapeutic agent and a pectin with a low DE, which gel is obtainable by applying a liquid composition, comprising said therapeutic agent and pectin in an aqueous carrier, to a mucosal surface, and which gel is substantially free of divalent metal ions derived from an extraneous source applied to said mucosal surface before, or at the same time as, or after, said liquid composition is applied.

Because the compositions of the invention are not added in conjunction with an extraneous source of such ions, by "substantially free" of divalent metal ions, we mean greater than 97%, preferably greater than 99%, more preferably greater than 99.9%, and especially greater than 99.99% free.

Pectins with a low DE can be obtained from known sources, or can be obtained *via* de-esterification of high DE pectins (which may be obtained from, for example, Sigma Fine Chemicals), in accordance with known techniques, such as those described in the article by Rollin in "*Industrial Gums*", Academic Press, New York (1993) p. 257, or as described hereinbefore. Low DE pectin may, for example, be obtained from Copenhagen Pectin A/S as the commercial material known as Slendid Type 100 and Slendid Type 110. These pectins have been extracted from citrus peel and standardised by the addition of sucrose. The

standardisation process is as described by Rollin in the abovementioned article. The DE is less than 50% for both pectins and of the order of 10% for type 100 and 35% for type 110. Further materials which may be employed include GENU pectin types LM 1912 CS and Pomosin pectin types LM 12 CG and LM 18 CG.

The compositions of the invention may be prepared by dissolving or dispersing the pectin of low DE and therapeutic agent in an aqueous system, to form a solution, a suspension or an emulsion in accordance with known techniques. For example, the therapeutic agent may be dissolved in a prior prepared aqueous solution of the pectin, or may be added as, or to form, a suspension in an aqueous system, where the drug particles are less than 100 microns in size, preferably between 1 and 20 microns. Alternatively, drug may be dissolved or suspended in a suitable oily vehicle such as a vegetable oil, and then dispersed into the aqueous pectin solution to form an emulsion. It will be appreciated by those skilled in the art that the type of aqueous formulation so developed will depend upon to mucosa to be treated, as well as the dose, and the physical characteristics and properties, of the drug (e.g. its solubility, basicity etc.).

The concentration of low DE pectin in compositions of the invention depends upon the nature of the pectin, the presence of other components, and other factors which influence gelation properties of the composition (see below), but may be from 1 g/L to 100 g/L, and is preferably from 1 g/L to 50 g/L, more preferably from 2 g/L to 10 g/L and especially from 5 g/L to 10 g/L.

Compositions of the invention may be used with a view to the prevention of a major problem in the delivery of drugs to the nose for local treatment, namely the rapid mucociliary clearance mechanism. This natural process, which removes deposited material from the front of the nose to the throat, can clear material from the nose with a half-time of about 10 to 20 minutes. Such clearance rates can be measured readily in man using the saccharin clearance test or by gamma scintigraphy (Aspden *et al*, J. Pharm. Sci., **86**, 509 (1997); Illum *et al*, Int. J. Pharm., **39** (1987) 189-199).

Compositions of the invention may be employed to retain a therapeutic agent which is intended to act locally at a mucosal surface for a relatively long period when compared to mucosal delivery systems known in the art. If the therapeutic agent is easily absorbed, absorption may be retarded, thus keeping more of the drug at the site of application, where it is needed.

Therapeutic agents which may be employed in the compositions of the invention include, for nasal administration, drugs that are employed locally to treat conditions such as rhinitis, viral infections, as well as those which act as decongestants. The compositions of the invention may also be used as a way of improving the delivery of vaccines to the nose associated lymphoid tissue and for the better presentation of DNA for the transfection of nasal epithelial cells.

The following list of therapeutic agents are suitable for use in the compositions of the invention, for local treatment of a mucosal surface, is provided by way of illustration and is not meant to be exclusive: antiviral agents such as ICAM-1, pirovadir, acyclovir, bromovinyldeoxyuridine, α,

β and γ-interferon, zidovudine; decongestants such as oxymetazaline; anti-allergic agents, such as sodium cromoglycate and budesonide; steroids, such as fluticazone; vaccines, such as DNA, influenza, pertussis, measles and diphtheria vaccines; antibacterial agents; antifungal agents, such as amphotericin, nystatin; contraceptive and/or spermicidal agents; antibodies especially for the treatment of RSV infection in children; prophylactic agents against HIV; antihistamines, such as diphenhydramine hydrochloride; genes.

Combinations of the abovementioned therapeutic agents may also be employed.

Compositions of the invention may also be employed to control the plasma level *versus* time profile for readily absorbable drugs which are intended to act systemically (ie. to give a flatter profile), either by altering the rate of transport into the general circulation, or by retarding absorption of readily absorbable drugs. This can, for example, be of importance when side effects from high peak plasma levels are to be avoided.

The compositions of the invention may thus be used for the modification of the systemic absorption of mucosally administered drugs, including, but not limited to, apomorphine, nicotine, hyoscine hydrobromide, lignocaine, fentanyl, naratriptan, pheromones and propranolol.

Combinations of the abovementioned therapeutic agents may also be employed.

For the avoidance of doubt, the term "therapeutic agents" is intended herein to include agents which are suitable for use in the treatment, and in the prevention, of disease.

The compositions of the invention may be used to treat/prevent diseases/conditions in mammalian patients depending upon the therapeutic agent(s) which is/are employed. For the above, non-exhaustive lists of locally acting and systemic drugs, diseases/conditions which may be mentioned include those against which the therapeutic agent(s) in question are known to be effective, and include those specifically listed for the drugs in question in Martindale, "*The Extra Pharmacopoeia*", 31st Edition, Royal Pharmaceutical Society (1996).

Preferred drugs include nicotine and apomorphine.

The amount of therapeutic agent which may be employed in the compositions of the invention will depend upon the agent which is used, and the disease to be treated, but may be in the range 0.01 to 40% w/w. However, it will be clear to the skilled person that suitable doses of therapeutic agents can be readily determined non-inventively. For example, estimates of dosage can be made from known injectable products assuming that from 0.1 to 90% of the dose is absorbed. Suitable single unit doses are in the range 10 μg to 500 mg depending upon the therapeutic agent(s) which is/are employed and the route of administration. Suitable daily doses are in the range 10 μg to 1 g/day depending upon the therapeutic agent(s) which is/are employed and the route of administration.

Most compositions comprising drug and a low DE pectin will gel upon application at the site of application, i.e. upon, or shortly (e.g. up to 5

minutes) after, contact with the relevant mucosal surface. However, in some formulations, the nature of the drug and/or the pectin which is/are employed may require that the composition is adapted such that it gels upon, or shortly (e.g. up to 1 minute) after, contact. This may be achieved readily *via* techniques which are well known to those skilled in the art:

For example, the concentration of pectin may be selected such that the aqueous formulation will gel once in contact with the mucosal surface.

Furthermore, the addition of monovalent ions to aid the gelling process may be required (for example, simple monovalent electrolytes, eg. NaCl, may be added to adapt the liquid formulation to gel, as well as to provide isotonicity).

The quantity and nature of the drug in the aqueous formulation may also have an influence on the gelation properties. For example, the addition of a high level of a certain drugs, including those which are weak bases (such as nicotine), which are known to form reversible complexes with anionic materials such as pectin, may require a change in the ratio between drug and pectin, so that preferably 30%, more preferably 50%, and most preferably 60%, of the negative charges on the pectin molecule are uncomplexed.

Alternatively, sugars in the form of, for example, sucrose can be added to the formulation to aid gelation. Non-ionic polysaccharides (such as hydroxypropyl methyl cellulose) may also be used.

The pH of the composition has also been found to affect gelation properties. The pH of the compositions of the invention may be from 2 to

9, more preferably from 3 to 8 and most preferably from 4 to 7, taking into account the gelation properties of the composition and the properties of the therapeutic agent. For example, in general, we have found that the lower the DE of the pectin, the lower the pH at which the composition will gel. pH may be adjusted in accordance with techniques which will be well known to those skilled in the art, such as the addition of pharmaceutically acceptable buffering agents, especially those of low ionic strength. Axelos and Thibault in "*The Chemistry and Technology of Pectin*", Academic Press, New York, pp. 109-118, (1991) describe how the gelation properties of low DE pectin solutions are somewhat sensitive to pH and ionic strength.

The abovementioned techniques, which may be used to adapt the compositions of the invention to gel, may be investigated and determined in the normal course of routine experimentation by those skilled in the art. Combinations of these techniques may also be employed in order to affect gelation properties.

The compositions may also contain other additives in the form of pharmaceutical excipients, such as preservatives (e.g. low concentrations of materials such as sodium metabisulphate), stabilisers, flavouring agents, absorption enhancers such as bile salts, phospholipids, as well as agents which are known to interact with the drug, for example to form inclusion or salt-bridge complexes, and promote a controlled release in the nasal cavity from the formed gel, such as cyclodextrins and ion exchange resins. Additional pharmaceutically acceptable excipients which may be added to the compositions of the invention include agents such as glycerol.

According to a further aspect of the invention there is provided a process for the preparation of a composition of the invention which comprises mixing together the therapeutic agent and the pectin in the aqueous carrier.

The compositions of the invention may be administered in suitable dosage forms, in accordance with techniques, and *via* delivery devices, all of which are known to those skilled in the art. For example, for nasal delivery, the compositions of the invention are preferably administered by way of a spray device, for example the Pfeiffer metered dose pump or the Valois metered dose pump, or *via* a liquid free flow system (such as nasal drops). For vaginal and rectal administration (infusion) a syringe-type applicator may be used, or plastics ampoules fitted with a suitable nozzle, where the contents of the ampoule can be delivered to the vaginal or rectal surface *via* the application of a slight pressure. Suitable systems for delivery of the compositions of the invention to the back of the throat include spray devices which are well known to those skilled in the art. Suitable systems for delivery of the compositions of the invention to eye include liquid free flow system which are well known to those skilled in the art (such as eye drops).

The compositions of the invention have the advantage that they may be readily administered to mucosal surfaces in the form of single component, simple liquid formulations, in the absence of an additional component comprising an extraneous source of divalent metal ions, using devices which are well known to those skilled in the art. The compositions of the invention also have the advantage that they gel upon, or shortly after, contact with mucosa, at physiologically acceptable pHs, in the presence of endogenous calcium (only) found physiologically in the nasal secretions,

as well as in the vaginal lumen, the rectal cavity and the tear fluid of the eye.

Compositions of the invention also have the advantage that they may be used to retain a locally-acting drug at a mucosal surface, or to control drug absorption into the systemic circulation.

Compositions of the invention may also have the advantage that they may be well accepted by patients, and may comprise materials that are approved by regulatory authorities.

According to a further aspect of the invention there is provided a method of treatment of a patient which comprises the administration of a liquid pharmaceutical composition, comprising a therapeutic agent, a pectin with a low DE and an aqueous carrier, which composition gels or is adapted to gel at the site of application, to a mucosal surface of said patient in the absence of extraneous application of a solution of divalent metal ions to said surface.

There is provided further a method of treatment or prophylaxis of a disease which comprises administration of a composition of the invention including a therapeutic agent which is effective against said disease to a mucosal surface of a patient in need of such treatment in the absence of extraneous application of a solution of divalent metal ions to said surface.

The invention is illustrated, but in no way limited, by the following examples with reference to the figures in which:

Figure 1 shows the effect of systemic uptake of salmon calcitonin when administered intranasally to sheep in formulations comprising low DE pectin.

Figure 2 shows the cumulative release/diffusion of fexofenadine HCl from HP-β-CD and HP-β-CD/pectin 100 solutions to simulated nasal electrolyte solution.

Example 1

To Demonstrate that Pectins with Low DEs Gel Under Simulated Conditions of the Nasal Cavity while Pectins with Higher DEs Do Not

Materials:

Pectin, esterified, potassium salt (DE: 31%; lot 22H0548; Sigma)

Pectin, esterified, potassium salt (DE: 67%; lot 74H1093; Sigma)

Pectin, esterified (DE: 93%; lot 125H0123; Sigma).

Pectin, Slendid type 100 (lot 620970; Hercules; Denmark).

Pectin, Slendid type 110 (lot 626790; Hercules, Denmark).

Pectin, GENU type LM 12 CG (lot G 63481; Pomosin GmbH; Hercules;, Germany).

Pectin, GENU type LM 18 CG (lot G 63484; Pomosin GmbH; Hercules; Germany).

Sodium chloride (BDH).

Potassium chloride (BDH).

Calcium chloride dehydrate (Sigma).

A simulated nasal electrolyte (SNES) solution was prepared, composed of the following ingredients:

Sodium chloride	8.77 g/L
Potassium chloride	2.98 g/L
Calcium chloride dehydrate	0.59 g/L

The SNES was prepared in double strength:

- 3.508 g of sodium chloride, 1.192 g of potassium chloride and 0.236 g of calcium chloride dehydrate were weighed into three weighing boats respectively, and
- dissolved and transferred into a 200 mL volumetric flask.
- The solution was stirred on a magnetic stirrer until the drug had dissolved.
- Water was added to volume.

Preparation of 20 g/L pectin solutions

- 1 g of each type of pectin was weighed into a 100 mL bottle.
- 50 mL of ultrapure water was added to each bottle.
- The content was stirred on a magnetic stirrer until pectin had dissolved, and
- the pH of the solution was measured and adjusted to pH 4 or pH 6.5 with 0.1M sodium hydroxide solution.

Preparation of various formulations containing SNES and pectin with different concentrations (2 to 10 g/L)

- Appropriate volumes of 20 g/L pectin solution, to obtain the final concentrations of 2, 3, 4, 5, 6, 7, 8, 9 and 10 g/L, were measured in a series of 10 mL screw capped glass tubes.

- Appropriate volumes of water were added to obtain a total volume of 2.5 mL firstly, then 2.5 mL of the two fold concentration SNES was added.
- The tubes were cooled in an ice water bath for 15 minutes.
- The test tubes were tilted to check the phase state and flow property.
- The tubes were vigorously shaken to check the phase state and flow property again.

Results

The results are shown in Table 1:

1. Pectin type 100 and 110 gelled with simulated nasal electrolyte solution when the final concentration of pectin was > 2 g/L and formed a strong gel when the final concentration was > 4 g/L at pH values of 4 and 6.5. The gel was transparent and homogeneous. The strength of gel increased with the increasing pectin concentration in system.

2. Pectin type LM 12 CG and LM 18 CG gelled at final pectin concentrations of 4 g/L and 6 g/L (pH 4) and 4 g/L (pH 6.5) respectively. These two pectin types only formed solid gels at pH 6.5 and at concentrations higher than 6 g/L and 8 g/L respectively.

3. Pectin with a DE of 31% (Sigma) gelled at a concentration of > 2 g/L and formed a solid gel at concentrations > 4 g/L. Pectin 67% and 93% did not form solid gels at concentrations up to 10 g/L at neither pH 4 nor at pH 6.5.

Summary of simulated nasal electrolyte solution (SNES) - pectin system

Table 1

Supplier	Pectin type	Esterification degree (%)	pH of 20 g/l pectin	The lowest pectin concentration for gelling (g/l)	The lowest pectin concentration for forming a solid gel (g/l)
Hercules (Denmark)	SLENDID type 100	15	4.25 (original pH)	2	4
			6.50 (adjusted pH)	2	4
	SLENDID type 110	35	4.01 (original pH)	2	4
			6.50 (adjusted pH)	2	4
POMOSIN GmbH Hercules (German)	Type LM 12 CG	35	2.75 (original pH)*		
			4.01 (adjusted pH)**	4	
			6.50 (adjusted pH)	4	6
	Type LM 18 CG	40	2.74 (original pH)*		
			4.00 (adjusted pH)**	6	
			6.50 (adjusted pH)	4	8

* Gelling had not happened when the final concentration of pectin was varied from 2 to 10 g/l
** A solid gel had not formed when the final concentration of pectin was varied from 2 to 10 g/l

Supplier	Pectin type	Esterification degree (%)	pH of 20 g/l pectin	The lowest pectin concentration for gelling (g/l)	The lowest pectin concentration for forming a solid gel (g/l)
Sigma	Esterified Potassium salt	31	5.13 (original pH)	2	4
			6.50 (adjusted pH)	2	4
	Esterified Potassium salt	67	4.62 (original pH)**	9	
			6.50 (adjusted pH)**	9	
	Esterified	93	2.88 (original pH)*		
			4.00 (adjusted pH)*		
			6.50 (adjusted pH)*		

*Gelling had not happened when the final concentration of pectin was varied from 2 to 10 g/l.
** A solid gel had not formed when the final concentration of pectin was varied from 2 to 10 g/l

Example 2

Nasal Drug Formulation Prepared from Pectins with Low DEs

Formulations were prepared containing drugs in the form of nicotine (a weak base) and cromolyn sodium (sodium cromoglycate; a weak acid). Pectin formulations were prepared at a pectin concentration of 10 mg/mL using Slendid 100 and Slendid 110. The formulations were mixed with the simulated nasal electrolyte solution (the method of preparation of which was as in Example 1). The formulations were filled into a nasal delivery device (Pfeiffer metered dose pump) and the spray properties evaluated by visual examination.

The gelation of the formulation in the nasal electrolyte solution was evaluated as solution, gel or solid by visual observation and the flow properties before and after shaking. The results, which are set out in Table 2, show that when the formulation contained a weak acid (cromolyn sodium), gelation occurred in the nasal electrolyte solution. When the formulation contained a high level of a weak base (nicotine) then gelation did not occur.

The applicants believe that the reason for this difference is that the ionised nicotine may interact with the charged carboxyl groups on the pectin molecules and thereby influence the gelation characteristics of the low esterified pectin. Thus, with weakly basic drugs, a person skilled in the art is able to adjust the pectin concentration to take this interaction into account (see above).

Table 2

Name	Sample	Spray property	Mixing with simulated nasal electrolyte solution		
			Phase state	Flow Property	Phase state after shaking
G1	10 mg/ml pectin Slendid 100	Good	Gel	-	Sol
G2	10 mg/ml pectin Slendid 110	Good	Gel	-	Sol
G3	Formulation I	Good	Sol	+++	Sol
G4	Formulation II	Good	Sol	+++	Sol
G5	Formulation III	Good	Gel	-	Sol
G6	Formulation IV	Good	Gel	-	Sol

Formulation I: 30.77 nicotine dihydrogen tartrate (10 mg/ml nicotine base) 10 mg/ml pectin 100
Formulation II: 30.77 nicotine dihydrogen tartrate (10 mg/ml nicotine base) 10 mg/ml pectin 110

Formulation III: 40 mg/ml cromolyn sodium salt/10 mg/ml pectin Slendid 100
Formulation IV: 40 mg/ml cromolyn sodium salt/10 mg/ml pectin Slendid 110

Flow properties: - : non-flowing; +++ : flowing

Example 3

To Demonstrate that Nasal Formulations containing Low DE Pectin do not Enhance the Systemic Uptake of a Poorly Absorbed Drug

For the local delivery of drugs it is important to retain the drug at its site of action, namely the nasal, rectal and vaginal cavities. In such cases, the formulation should not enhance the absorption of the drug. It is known that some bioadhesive gelling formulations may increase systemic uptake. Therefore, experiments have been conducted in an animal model to demonstrate that pectins with low DE do not enhance the nasal uptake (systemically) of a model polar drug, salmon calcitonin (S-CT).

Sheep

Eight female, cross-bred sheep of known weight were used in this study. The average weight of the sheep was in the region of 60 kg. The sheep were weighed and labelled 1 to 8. An in-dwelling Secalon cannula fitted with a flowswitch was placed approximately 15 cm into one of the external jugular veins of each animal on the first day of the study. Whenever necessary, the cannula was kept patent by flushing it with heparinised (25 IU/mL) 0.9% saline solution. This cannula remained in-dwelling in the jugular vein of each animal for the duration of the study and was removed upon completion of the study.

Preparation of salmon calcitonin (S-CT) formulations

Two S-CT formulations were prepared. Each formulation contained 2000 IU/mL S-CT, which was sufficient material to administer a dose of 20 IU/kg in a volume of 0.01 mL/kg. The sheep were randomly divided into

two groups of four animals and each group was dosed with a different S-CT formulation.

Summary of the dose groups

Formulation	S-CT (IU/kg)	Chitosan G210 (mg/kg)	Pectin Slendid 100 (mg/kg)
I	20	-	-
II	20	-	0.1

Prior to dose administration the sheep were sedated with an intravenous dose of Ketamine Vetalar® (100 mg/mL injection) at 2.25 mg/kg. Intranasal doses were administered at 0.01 mL/kg. The dose was divided equally between each nostril. For dose administration, a blueline umbilical cannula was inserted into the nostril of the sheep to a depth of 10 cm, before the delivery of the appropriate volume of solution from a 1 mL syringe.

Blood sampling

Blood samples of 4 mL were collected from the cannulated jugular vein of the sheep at 15 and 5 minutes prior to S-CT administration and at 5, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 480 minutes post-administration. They were then mixed gently in 4 mL heparinised tubes and kept on crushed ice before plasma separation. Plasma was separated by centrifugation for 10 minutes at 4°C approximately 3000 rpm. Each plasma sample was divided into two equal aliquots of approximately 1 mL and stored at -20°C. One set of plasma samples was used for calcium analysis.

Calcium analysis

Plasma calcium analysis was performed by the Clinical Chemistry Department, Queens Medical Centre, University of Nottingham. The results showed that for the formulation I and II the plasma calcium levels were very similar and that the presence of pectin in the formulation did not lead to an increase in the systemic bioavailability of the model drug.

Example 4

Simulated Nasal Electrolyte Solution-Pectin Gelling System for Controlled Release of Fexofenadine Hydrochloride

Preparation of Formulations

Formulation 1 - 10 mg/mL fexofenadine HCl/100 mg/mL HP-β-CD:
2 g of HP-β-CD was dissolved in 18-19 mL of water in a 20 mL volumetric flask. 200 mg of fexofenadine was added to the solution and stirred until the drug has dissolved. The pH of the solution was adjusted to 4.0, then the solution was made up to volume with water.

Formulation 2 - 10 mg/mL fexofenadine HCl/100 mg/mL HP-β-CD/10 mg/mL pectin 100:
50 mg of pectin 100 (SLENDID type 100, Hercules, Denmark) was dissolved in 5 mL of Formulation 1 in a 5 mL volumetric flask.

Release/Diffusion Testing

A Franz diffusion cell apparatus was set up in a closed loop arrangement and parameters were listed as follows:

Medium: Simulated nasal electrolyte solution

Temperature: 37°C

Membrane: Cellulose nitrate, 0.45 μm pore size

Volume of the closed loop arrangement: 8.8 mL

Stirring speed of a magnetic stirrer: 4

Peristaltic pump flow rate: 1 (The Cole-Parmer Masterflex peristaltic pump, Model 7518-60, fitted with Masterflex L/Sth 14 silicone tubing)

Sample volume: 0.4 mL (contained 4 mg of fexofenadine HCl, the maximum concentration of the drug in medium will be around 450 μg/mL)

Wavelength: 260 nm

Results

The results are shown in Figure 2. (Every point on the graphs represents a mean value of two points.)

The maximum UV absorbance of Formulation 1 (control) reached during the diffusion experiment was used as 100% release to calculate the percentage of release at each selected time point.

The results show a clear difference in release characteristics of the two formulations.

Claims

1. A single component liquid pharmaceutical composition for administration to a mucosal surface comprising a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier, that gels or can be adapted to gel at the site of application.

2. A composition as claimed in Claim 1, wherein the mucosal surface is the nasal cavity.

3. A composition as claimed in Claim 1, wherein the mucosal surface is the vagina.

4. A composition as claimed in Claim 1, wherein the mucosal surface is the rectum.

5. A composition as claimed in Claim 1, wherein the mucosal surface is the back of the throat.

6. A composition as claimed in Claim 1, where the mucosal surfaces is the eye.

7. A composition as claimed in any one of the preceding claims which is administered as a spray or a liquid free flowing system.

8. A composition as claimed in any one of the preceding claims wherein the degree of esterification is less than 50%.

9. A composition as claimed in any one of the preceding claims, wherein the pectin concentration in the composition is from 1 to 100 g/L.

10. A composition as claimed in any one of the preceding claims, wherein the pH of the composition is between 2 and 9.

11. A composition as claimed in any one of Claims 1 to 3 or 7 to 10, for use in the delivery of an antiviral agent to the nose or the vagina.

12. A composition as claimed in any one of Claims 1 to 4 or 7 to 10, for use in the delivery of a vaccine to the nose, the rectum or the vagina.

13. A composition as claimed in any one of Claims 1, 2 or 7 to 10, for use in the delivery of a decongestant agent.

14. A composition as claimed in any one of Claims 1, 3 or 7 to 10, for use in the delivery of a contraceptive agent.

15. A composition as claimed in any one of Claims 1, 3, 7 to 12 or 14, for use as a vaginal lubricating agent.

16. A composition as claimed in any one of Claims 1 to 10 for use in the delivery of an anti-allergic agent.

17. A pharmaceutical formulation in a form suitable for administration to a mucosal surface, which formulation comprises a composition according to any one of Claims 1 to 16 in a pharmaceutically acceptable dosage form.

18. A formulation as claimed in Claim 17 which is in the form of a spray or a liquid free flowing system.

19. The use of a composition according to any one of Claims 1 to 16, or a formulation according to Claim 17 or Claim 18, as a means of delivery of therapeutic agents to the nose, the vagina, the rectum, the back of the throat or the eye.

20. A kit of parts comprising a liquid pharmaceutical composition for administration to a mucosal surface, comprising a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier, which composition gels or is adapted to gel at the site of application, provided that the kit does not comprise a solution of divalent metal ions to be added extraneously to said surface.

21. A kit of parts comprising a liquid pharmaceutical composition for administration to a mucosal surface, which composition comprises a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier, which composition gels or is adapted to gel at the site of application, and which kit of parts is packaged and presented with instructions to administer said composition to said surface in the absence of an extraneous source of divalent metal ions.

22. A kit of parts comprising a composition according to any one of Claims 1 to 16, or a formulation according to Claim 17 or Claim 18, which kit of parts is packaged and presented with instructions to administer the composition or formulation to a mucosal surface in the absence of an extraneous source of divalent metal ions.

23. A pharmaceutical gel composition obtainable by applying a liquid composition, comprising a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier, to a mucosal surface of a mammalian patient in the absence of extraneous application of a solution of divalent metal ions to said surface.

24. A pharmaceutical gel composition comprising a therapeutic agent and a pectin with a low dgeree of esterification, which gel is obtainable by applying a liquid composition, comprising said therapeutic agent and pectin in an aqueous carrier, to a mucosal surface, and which gel is substantially free of divalent metal ions derived from an extraneous source applied to said mucosal surface before, or at the same time as, said liquid composition is applied.

25. A pharmaceutical gel composition obtainable by administering a composition according to any one of Claims 1 to 16, a formulation according to Claim 17 or Claim 18, or a composition of a kit according to any one of Claims 20 to 22, to a mucosal surface of a mammalian patient in the absence of extraneous application of a solution of divalent metal ions to said surface.

26. A method of treatment of a patient which comprises the administration of a liquid pharmaceutical composition, comprising a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier, which composition gels or is adapted to gel at the site of application, to a mucosal surface of said patient in the absence of extraneous application of a solution of divalent metal ions to said surface.

27. A method of treatment or prophylaxis of a disease which comprises administration of a liquid pharmaceutical composition, comprising a therapeutic agent which is effective against said disease, a pectin with a low degree of esterification and an aqueous carrier, which composition gels or is adapted to gel at the site of application, to a mucosal surface of a patient in need of such treatment, in the absence of extraneous application of a solution of divalent metal ions to said surface.

28. A method for delivering a therapeutic agent in a liquid formulation to the nose, eye, rectum, back of throat or vagina which comprises the delivery of said agent in a composition according to any one of Claims 1 to 16.

29. A method of treatment of a mammalian patient which comprises administration of a composition according to any one of Claims 1 to 16 to such a patient.

30. A method for the delivery of therapeutic agents to a mucosal surface in a mammal, which comprises administering a composition, as defined in any one of Claims 1 to 16 to said surface.

31. The use of a composition according to any one of Claims 1 to 16, a formulation according to Claim 17 or Claim 18, or a kit according to any one of Claims 20 to 22, as a means of delivery of therapeutic agents to the nose, vagina, rectum, back of the throat, or eye.

32. The use of a composition according to any one of Claims 1 to 16 in the manufacture of a medicament for the delivery of a therapeutic agent to the nose, vagina, rectum, back of the throat, or eye.

33. The use of a composition according to any one of Claims 1 to 16 in the manufacture of a medicament for the treatment or prophylaxis of a disease which comprises administration of said composition, including a therapeutic agent which is effective against said disease, to a mucosal surface of a patient in need of such treatment or prophylaxis, in the absence of extraneous application of a solution of divalent metal ions to said surface.

34. The use of a pectin with a low degree of esterification in the manufacture of a single component liquid composition for the delivery of therapeutic agents to mucosal surfaces.

35. The use of a composition according to any one of Claims 1 to 16 in the manufacture of a medicament for use in a method of treatment according to any one of Claims 26 to 30.

36. A composition comprising a therapeutic agent, a pectin with a low degree of esterification and an aqueous carrier, which composition is packaged and presented for use in the treatment of a patient, which treatment comprises the administration of said composition to a mucosal surface of said patient in the absence of extraneous application of a solution of divalent metal ions to said surface.

37. The use of a pectin with a low degree of esterification in the manufacture of an aqueous liquid pharmaceutical composition for the treatment of a patient comprising the administration of said composition to a mucosal surface of said patient in the absence of extraneous application of a solution of divalent metal ions to said surface.

38. A process for the preparation of a composition according to any one of Claims 1 to 16, a composition of a formulation according to Claim 17 or Claim 18, or a composition of a kit according to any one of Claims 20 to 22, which comprises mixing together the therapeutic agent and the pectin in the aqueous carrier.

39. A product obtainable by a process according to Claim 38.

Figure 1

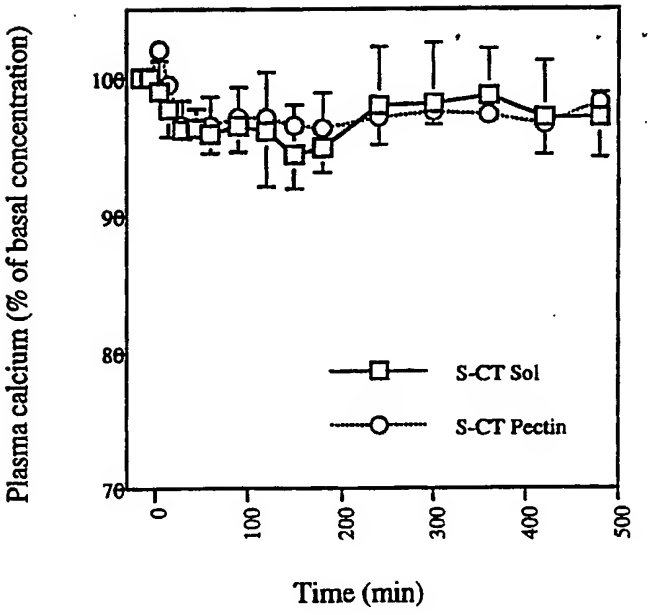
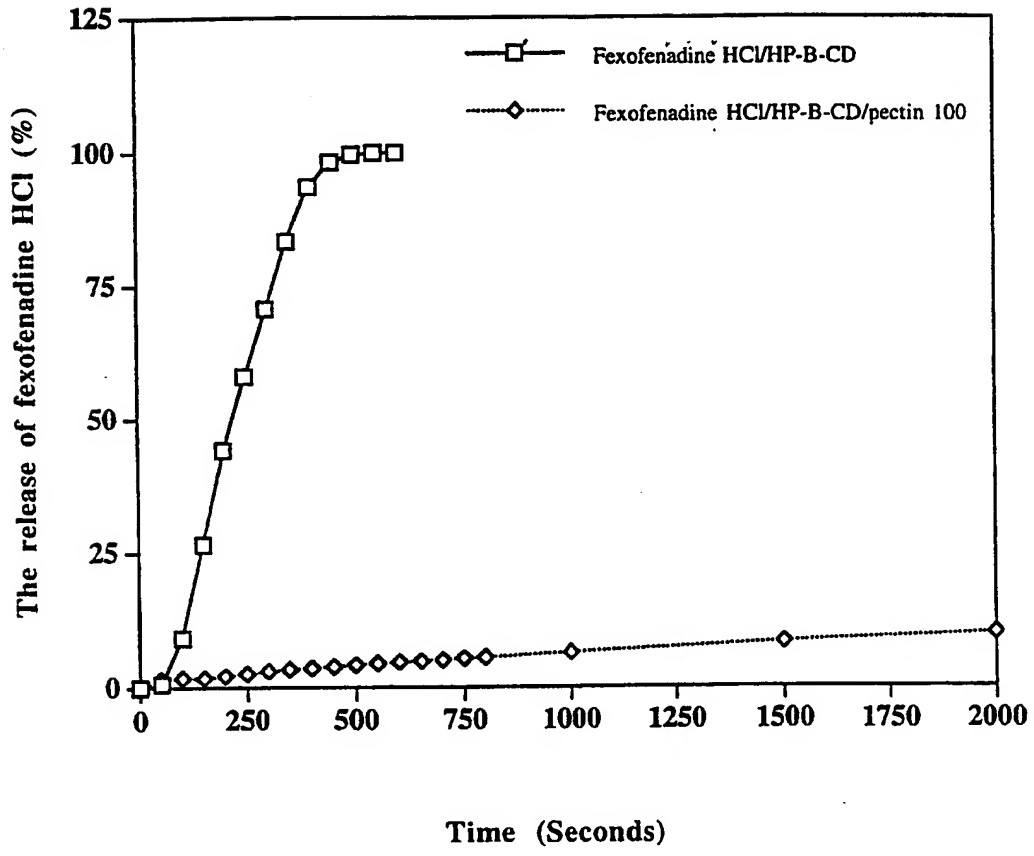

Plasma calcium (% of basal concentration)
100
90
80
70
0
100
200
300
400
500
Time (min)
S-CT Sol
S-CT Pectin

Figure 2


125
100
75
50
25
0
0
250
500
750
1000
1250
1500
1750
2000
The release of fexofenadine HCl (%)
Time (Seconds)
Fexofenadine HCl/HP-B-CD
Fexofenadine HCl/HP-B-CD/pectin 100

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 98/01147

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/36 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 457 093 A (CINI JOHN K ET AL) 10 October 1995	
A	EP 0 518 798 A (CHEMEX BLOCK DRUG JV) 16 December 1992	
A	US 4 915 948 A (GALLOPO ANDREW R ET AL) 10 April 1990	
A	US 4 983 385 A (HASEGAWA KENJI ET AL) 8 January 1991	
A	US 5 456 745 A (ROREGER MICHAEL ET AL) 10 October 1995	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the International search report
31 August 1998	09/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/01147

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 19, 26-33
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/01147

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5457093 A	10-10-1995	US 5427778 A	27-06-1995
		US 5705485 A	06-01-1998
		AU 2223588 A	23-03-1989
		EP 0312208 A	19-04-1989
		GR 88100617 A,B	22-06-1989
		JP 2000112 A	05-01-1990
		MX 169808 B	27-07-1993
		PT 88541 A	31-07-1989
EP 0518798 A	16-12-1992	CA 2065496 A	10-10-1992
		EP 0836852 A	22-04-1998
		JP 5097706 A	20-04-1993
US 4915948 A	10-04-1990	AR 240248 A	30-03-1990
		AU 2005988 A	02-03-1989
		EP 0306454 A	08-03-1989
		JP 1096117 A	14-04-1989
		PH 25488 A	24-07-1991
		PT 88369 A	30-06-1989
US 4983385 A	08-01-1991	JP 1804895 C	26-11-1993
		JP 5011092 B	12-02-1993
		JP 62123112 A	04-06-1987
US 5456745 A	10-10-1995	DE 3827561 C	28-12-1989
		AT 145226 T	15-11-1996
		CA 1336727 A	15-08-1995
		DE 58909748 D	19-12-1996
		EP 0355536 A	28-02-1990
		ES 2097111 T	01-04-1997
		GR 3022543 T	31-05-1997
		JP 2074259 C	25-07-1996
		JP 2088644 A	28-03-1990
		JP 7091397 B	04-10-1995